NDA 17-007/S-038

SEP 6 2000

Wyeth-Ayerst Laboratories
Attention: Ms. Mary Alice Dankulich
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Dankulich:

Please refer to your supplemental new drug application dated August 10, 1998, received August 11, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection, USP; Heparin Lock Flush Solution, USP; and Heparin Flush Kits (Heparin Lock Flush Solution, USP and Bacteriostatic Sodium Chloride Injection. USP).

We also refer to your submission dated December 29, 1998, received December 30, 1998, submitted in response to the Agency's September 15, 1998 refuse-to-file letter.

We acknowledge receipt of your submission dated August 3, 2000. That submission constituted a complete response to our July 16, 1999 action letter.

This supplement new drug application provides for the following: (1) in the PRECAUTIONS section, the addition of a "Geriatric Use" subsection, to the package insert in response to the Final Rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of 'Geriatric Use' Subsection in the Labeling," published in the August 27, 1997 Federal Register (62 FR 45313-45326); (2) in the PRECAUTONS section, the "General" subsection, the deletion of the "Increased Risk in Older Women" sub-subsection of the "Heparin Lock Flush Solution, USP" and the "Heparin Sodium Injection, USP" package inserts; (3) deletion of the statement "Caution: Federal law prohibits dispensing without prescription."; and (4) insertion of the phrase "Rx only" below the title section of the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in final printed labeling for the Heparin Sodium Injection, USP and the Heparin Lock Flush Solution, USP package inserts, submitted August 3, 2000. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

We note that the Heparin Flush Kits have been discontinued, and, therefore, the final printed labeling for the Heparin Flush Kits package insert was not included in the August 3, 2000 submission.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we' request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Karen Oliver, Regulatory Health Project Manager, at (301) 827-7457.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Heparin Lock Flush Solution, USP

L only

Heparin Lock Flush Solution is intended for maintenance of patency of intravenous injection devices only and is not to be used for anticoagulant therapy.

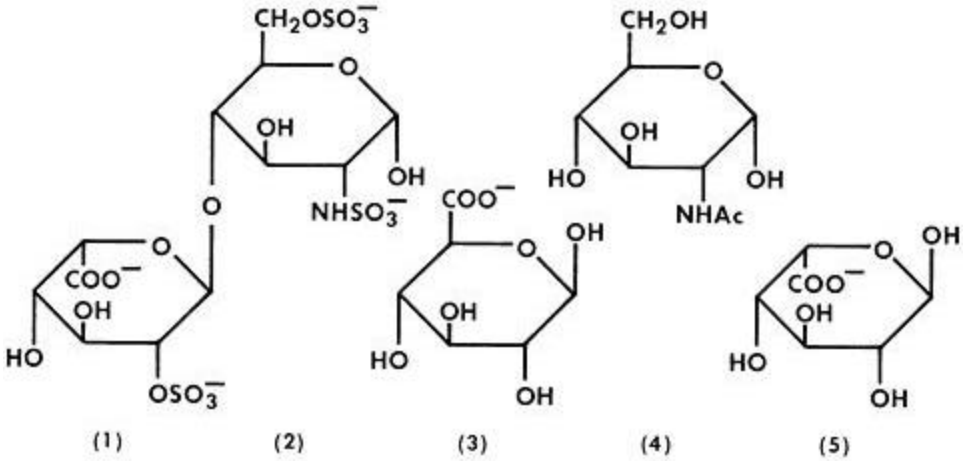
DESCRIPTION

TUBEX® Heparin Lock Flush Solution, USP is a sterile solution. Each mL contains either 10 or 100 USP units heparin sodium derived from porcine intestinal mucosa (standardized for use as an anticoagulant) in normal saline solution, and not more than 10 mg benzyl alcohol as a preservative. The pH range is 5.0 to 7.5.

The potency is determined by biological assay using a USP reference standard based upon units of heparin activity per milligram.

Heparin is a heterogenous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, having anticoagulant properties. Although others may be present, the main sugars occurring in heparin are: (1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-(alpha)-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2) > (1) > (4) > (3) > (5), and are joined by glycosidic linkages forming polymers of varying sizes. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions.

STRUCTURE OF HEPARIN SODIUM (representative subunits):



CLINICAL PHARMACOLOGY

Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo.* Heparin acts at multiple sites in the normal coagulation systems. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases, it is not measurably affected by low doses of heparin.

Loglinear plots of heparin plasma concentrations with time, for a wide range of dose levels, are linear which suggests the absence of zero order processes. Liver and the reticulo-endothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2}$ = 10 min.), and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

INDICATIONS AND USAGE

Heparin Lock Flush Solution, USP is intended to maintain patency of an indwelling venipuncture device designed for intermittent injection or infusion therapy or blood sampling. Heparin Lock Flush Solution, USP may be used following initial placement of the device in the vein, after each injection of a medication or after withdrawal of blood for laboratory tests. (See **DOSAGE AND ADMINISTRATION**, **Maintenance Of Patency Of Intravenous Devices**, for direction for use.)

Heparin Lock Flush Solution, USP is not to be used for anticoagulant therapy.

CONTRAINDICATIONS

Heparin sodium should not be used in patients with the following conditions:

severe thrombocytopenia; an uncontrollable active bleeding state (see **WARNINGS**), except when this is due to disseminated intravascular coagulation.

WARNINGS

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature neonates.

Neonatologists do not advise the use of 100 units/mL concentration because of the risk of bleeding, especially in low birth weight neonates.

Heparin is not intended for intramuscular use.

Hypersensitivity
Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations. (See **ADVERSE REACTIONS** , **Hypersensitivity**.")

Hemorrhage
Hemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure or any other unexplained symptom should lead to serious consideration of a hemorrhagic event.

Heparin sodium should be used with extreme caution in infants and in patients with disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exists are:

Cardiovascular --subacute bacterial endocarditis, severe hypertension.

Surgical --during and immediately following (a) spinal tap or spinal anesthesia or (b) major surgery, especially involving the brain, spinal cord, or eye.

Hematologic --conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia and some vascular purpuras.

Gastrointestinal --ulcerative lesions and continuous tube drainage of the stomach or small intestine.

Other --menstruation, liver disease with impaired hemostasis.

Thrombocytopenia
Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. Mild thrombocytopenia (count greater than 100,000/mm^3) may remain stable or reverse even if heparin is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100,000/mm^3 or if recurrent thrombosis develops (see **PRECAUTIONS** , **General**, *White-clot Syndrome* "), the heparin product should be discontinued. If continued heparin therapy is essential, administration of heparin from a different organ source can be reinstituted with caution.

PRECAUTIONS

General
In infants, the cumulative amounts of heparin and benzyl alcohol received from the frequent administration of Heparin Lock Flush Solution, USP during a 24-hour period should be considered.

Precautions must be exercised when drugs which are incompatible with heparin are administered through an indwelling intravenous catheter containing Heparin Lock Flush Solution, USP. (See " **Dosage and Administration** , MAINTENANCE OF PATENCY OF INTRAVENOUS DEVICES.")

White-clot Syndrome
It has been reported that patients on heparin may develop new thrombus formation in association with thrombocytopenia, resulting from irreversible aggregation of platelets

induced by heparin, the so-called "white-clot syndrome." The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

Increased Risk in Older Patients, Especially Women
A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.

Laboratory Tests
Periodic platelet counts, hematocrits and tests for occult blood in stool are recommended during the entire course of heparin use (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

Platelet Inhibitors
Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine, and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

Other Interactions
Digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium.

Carcinogenesis, Mutagenesis, Impairment Of Fertility
No long-term studies in animals have been performed to evaluate carcinogenic potential of heparin sodium. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

Pregnancy

Teratogenic Effects --Pregnancy Category C
Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects
Heparin does not cross the placental barrier.

Nursing Mothers
Heparin is not excreted in human milk.

Pediatric Use
Heparin Lock Flush Solution, USP is not recommended for use in the neonate (see **WARNINGS**).

Geriatric Use

Ahigher incidence of bleeding has been reported in patients 60 years of age, especially women (see **PRECAUTIONS, General** and **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

Hemorrhage

Hemorrhage is the chief complication that may result from heparin use (see **WARNINGS, Hemorrhage**). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see **OVERDOSAGE**).

Local Irritation

Local irritation and erythema have been reported with the use of Heparin Lock Flush Solution, USP.

Hypersensitivity

Generalized hypersensitivity reactions have been reported, with chills, fever, and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar side of the feet, may occur.

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. While often mild and of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications, such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. (See **WARNINGS** and **PRECAUTIONS**)

Certain episodes of painful, ischemic and cyanosed limbs have been attributed, in the past, to allergic vasospastic reactions. Whether these are, in fact, identical to the thrombocytopenia-associated complications remains to be determined.

OVERDOSAGE

Symptoms

Bleeding is the chief sign of heparin overdosage. Nosebleeds, blood in urine, or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

Treatment--Neutralization Of Heparin Effect

When clinical circumstances (bleeding) require reversal of heparinization, protamine sulfate (1% solution) by slow infusion will neutralize heparin sodium. No more than 50 mg should be administered, very slowly, in any 10-minute period. Each mg of protamine sulfate neutralizes approximately 100 USP heparin units. The amount of protamine required decreases over time as heparin is metabolized. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about $^{1}/_{2}$ hour after intravenous injection.

Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported,

the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For additional information consult the labeling of Protamine Sulfate Injection, USP products.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight discoloration does not alter potency.

Heparin Lock Flush Solution, USP is **not recommended for use in the neonate** (see **WARNINGS**).

Maintenance Of Patency Of Intravenous Devices

To prevent clot formation in a heparin lock set or central venous catheter following its proper insertion, Heparin Lock Flush Solution, USP is injected via the injection hub in a quantity sufficient to fill the entire device. This solution should be replaced each time the device is used. Aspirate before administering any solution via the device in order to confirm patency and location of needle or catheter tip. If the drug to be administered is incompatible with heparin, the entire device should be flushed with normal saline before and after the medication is administered; following the second saline flush, Heparin Lock Flush Solution, USP may be reinstilled into the device. The device manufacturer's instructions should be consulted for specifics concerning its use. Usually this dilute heparin solution will maintain anticoagulation within the device for up to 4 hours.

Note: Since repeated injections of small doses of heparin can alter tests for activated partial thromboplastin time (APTT), a baseline value for APTT should be obtained prior to insertion of an intravenous device.

Withdrawal Of Blood Samples

Heparin Lock Flush Solution, USP may also be used after each withdrawal of blood for laboratory tests. When heparin would interfere with or alter the results of blood tests, the heparin solution should be cleared from the device by aspirating and discarding it before withdrawing the blood sample.

The **TUBEX® BLUNT POINTE** ™ Sterile Cartridge Unit is suitable for substances to be administered intravenously. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. As of the date of this circular, **TUBEX BLUNT POINTE** is compatible with LifeShield® Prepierced Reseal injection site, Interlink® Injection Site, and SafeLine® Injection Site, User-Gard® Intermittent Injection Cap, and Safesite® reflux valve.

HOW SUPPLIED

Heparin Lock Flush Solution, USP is available in **TUBEX® BLUNT POINTE** ™ Sterile Cartridge Units and in **TUBEX®** Sterile Cartridge-Needle Units.

Each 1 mL size **TUBEX®** contains one of the following concentrations of heparin sodium, in packages of 50 **TUBEX®** :

10 USP Units per mL:

NDC 0008-0523-50, **BLUNT POINTE** ™.

NDC 0008-0523-01, (25 gauge × 5/8 inch needle).

100 USP Units per mL:

NDC 0008-0487-50, **BLUNT POINTE** ™.

NDC 0008-0487-01, (25 gauge × 5/8 inch needle).

Each 2.5 mL size **TUBEX®** contains one of the following concentrations of heparin sodium in packages of 50 **TUBEX®** :

25 USP Units per **TUBEX®** (10 USP Units per mL):

NDC 0008-0523-51, **BLUNT POINTE** ™.

NDC 0008-0523-02, (25 gauge × 5/8 inch needle).

250 USP Units per **TUBEX®** (100 USP Units per mL):

NDC 0008-0487-51, **BLUNT POINTE** ™.

NDC 0008-0487-03, (25 gauge × 5/8 inch needle).

Do not use if solution is discolored or contains a precipitate

Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP].

Do not freeze

Single use only. Discard any unused solution after initial use.

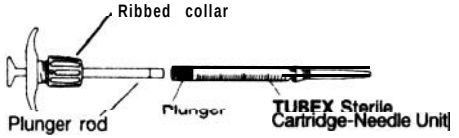
PLEASE NOTE: THE WYETH-AYERST METAL TUBEX HYPODERMIC SYRINGE AND TUBEX FAST-TRAK SYRINGE HAVE BEEN DISCONTINUED AND REPLACED BY THE TUBEX INJECTOR. EXCHANGE OF THESE DISCONTINUED SYRINGES IS AVAILABLE, FREE OF CHARGE, FROM YOUR WYETH-AYERST SALES REPRESENTATIVE, OR FROM WYETH-AYERST DIRECTLY. FOR LOADING AND UNLOADING INFORMATION ON THESE DISCONTINUED SYRINGES, CONTACT THE MEDICAL AFFAIRS DEPARTMENT, AT WYETH-AYERST LABORATORIES, P.O. BOX 8299, PHILADELPHIA, PA 19101.

TUBEX® Injector

NOTE: The TUBEX Injector is reusable: do not discard.

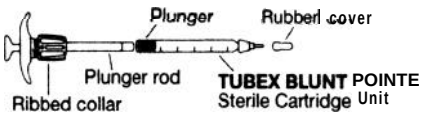
TUBEX Sterile Cartridge-Needle Unit

DIRECTIONS FOR USE:



TUBEX BLUNT POINTE Sterile Cartridge Unit

DIRECTIONS FOR USE:

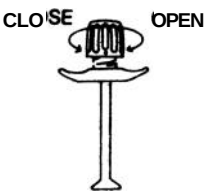


TUBEX BLUNT POINTE Sterile Cartridge Unit is intended for use with injection sets specifically manufactured as "needle-less" injection systems. As of the date of this circular, **TUBEX BLUNT POINTE** Sterile Cartridge Unit is compatible with LifeShield® Prepierced Reseal injection site, InterLink® Injection Site, SafeLine® Injection Site, User-Gard® Intermittent Injection Cap, and SafSite® reflux valve*. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" injection system.

NOTE: USE ASEPTIC TECHNIQUE FOR ALL MANIPULATIONS OF STERILE PARTS.

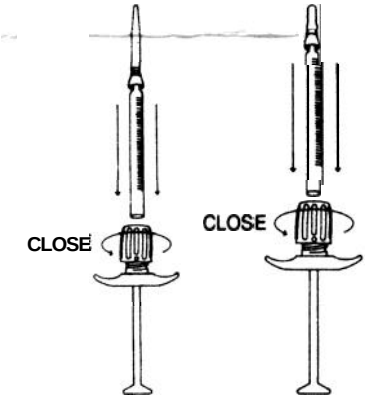
To load a TUBEX Sterile Cartridge Unit into the TUBEX Injector

1. Turn the ribbed collar to the "OPEN" position until it stops.



TUBEX Sterile Cartridge-Needle Unit

TUBEX BLUNT POINTE Sterile Cartridge Unit

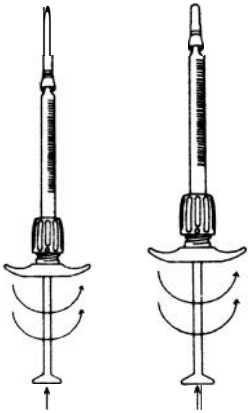


2. Hold the Injector with the open end up and fully insert the **TUBEX** Sterile Cartridge Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.

3. Thread the plunger rod into the plunger of the **TUBEX** Sterile Cartridge Unit until slight resistance is felt.

The Injector is now ready for use in the usual manner.

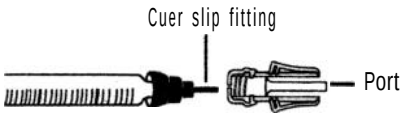


To administer TUBEX Sterile Cartridge-Needle Units

Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

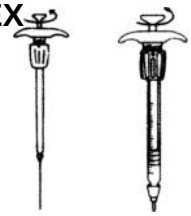
To administer TUBEX BLUNT POINTE Sterile Cartridge Units

"Needle-less" IV set administration is similar to administration with conventional syringes. Remove rubber cover by grasping it securely; twist and pull.



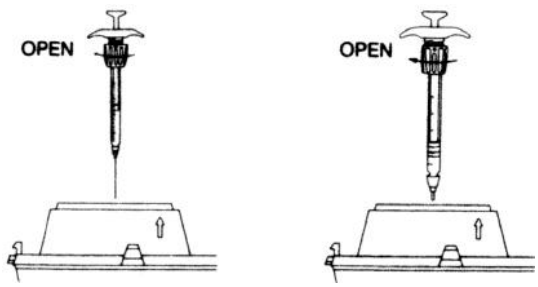
*For SafSite reflux valves, aseptically swab the Luer slip fitting of the **TUBEX BLUNT POINTE** sterile cartridge tip assembly with a sterile, individually wrapped, saturated 70% isopropyl alcohol swab. This action will remove the lubricant coating from the tip to facilitate a tight seal. Introduce **TUBEX BLUNT POINTE** Sterile Cartridge Unit into the "needle-less" IV set as per manufacturer's "Directions For Use."

To remove the empty TUBEX Cartridge Unit and dispose into a vertical disposal container



1. Do not recap the needle/ point. Disengage the plunger rod.

2. Hold the injector, needle/point down, over a vertical disposal container and loosen the ribbed collar. **TUBEX** Cartridge Unit will drop into the container.



3. Discard the cover.

To remove the empty TUBEX Cartridge Unit and dispose into a horizontal (mail-box) disposal container

1. Do not recap the needle/point. Disengage the plunger rod.

2. Open the horizontal (mailbox) disposal container. Insert **TUBEX** Cartridge Unit, needle/point pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar; **TUBEX** Cartridge Unit wiil drop into the container.

3. Discard the cover.

The **TUBEX** Iniector is reusable and should not be discarded.

Used **TUBEX** Cartridge Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded.

NOTE: Any graduated markings on **TUBEX** Sterile Cartridge Units are to be used only as a guide in administering doses.

Wyeth-Ayerst does not recommend and will not accept responsibility for the use of any cartridge-needle units or needle-less units other than TUBEX or E.S.I. DOSETTE Cartridge Units in the TUBEX Injector.

REFERENCES

Kappa, Jeffrey R., M.D. et al.: Heparin-induced platelet activation in sixteen surgical patients: Diagnosis and Management. Journal of Vascular Surgery 5(1):101-1 07, 1987.

King, Derek J. and Kelton, John G., M.D.: Heparin-associated thrombocytopenia. Annals of Internal Medicine 100:535-540, 1984.